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NATURAL PROGRESSION OF AORTIC STENOSIS IN A VETERAN POPULATION

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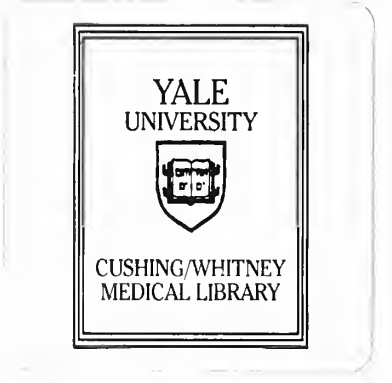
Yale University

1998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NATURAL PROGRESSION OF AORTIC STENOSIS IN A VETERAN POPULATION

A Thesis submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Marjory Alabre

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I. ABSTRACT

NATURAL PROGRESSION OF AORTIC STENOSIS IN A VETERAN POPULATION. Marjory Alabre and Michael Ezekowitz, Section of Cardiology, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.

To try to determine the rate of progression of aortic stenosis (AS) and the factors which can help predict its rate of progression, we looked at 109 patients with varying degrees of the disease, selected from the echo lab at the West Haven VA Medical Center. We studied them retrospectively and prospectively with respect to 9 risk factors: history of hypertension, smoking, cholesterol level>200, HDL<29, triglyceride level>160, NIDDM, IDDM, BUN>40, and creatinine>2. Data was collected from their echo charts, medical charts, and their computerized lab values. We then divided them into two groups depending on whether we were looking at the area under the aortic valve (AVA) or the peak aortoventricular (AV) gradient in order to determine progression. The groups comprised 32 and 69 patients, respectively (only patients who had had more than one measurement of the parameter under consideration qualified for inclusion). Next, t values, p values and

correlation coefficients were determined for the different factors studied, as well as different combinations of factors. Finally, a multiple regression analysis was carried out on all 32 patients in the AVA group.

Of the 32 patients in the AVA group, 21 (65.6%) were found to have progression of the disease, evidenced by a decrease in the AVA, over an average observation period of 15 months ± 6 (1 SD). Fifty eight (84%) of the 69 patients in the peak AV gradient group showed progression, demonstrated by an increase in the gradient, over an average of 4.6 years ± 2 (1 SD). The rates of progression were 0.35 cm^2/year ± 0.22 (1 SD) for the AV group and 6 mmHg/year ± 5.5 (1 SD) for the gradient group. The presence of a history of hypertension, smoking, cholesterol level>200, triglyceride level>160, NIDDM, and any two risk factors together were associated with a greater mean AVA decrease. Those results, however, were not statistically significant (p=NS). On the other hand, only a history of hypertension and NIDDM were associated with a greater mean peak AV gradient increase. Again, statistical analyses showed no significance (p=NS). Furthermore, multiple regression analysis also failed to show any statistical significance (p=NS).

We conclude that the rate of progression of aortic stenosis in this population was 0.35 cm^2/year ± 0.22 (1 SD) as measured by the AVA and 6 mmHg/year ± 5.5 (1 SD) as measured by the peak AV gradient. Although a

history of hypertension, smoking, cholesterol>200, triglyceride>160 and NIDDM seemed to be associated with a greater rate of AS progression, the associations were not statistically significant. Lastly, we discuss the limitations of our study, the major one being its low statistical power.

II. INTRODUCTION

A. DEFINITION

Valvular aortic stenosis is characterized by narrowing of the lumen of the ventriculoaortic opening and is especially common in the older population. There is a long period of low risk when patients are asymptomatic but once symptoms develop, their prognosis worsens tremendously. Aortic valve replacement usually improves symptoms and prolongs survival. However, in patients who do not undergo surgery, survival depends on the nature of the symptoms: 3 years after the onset of angina or syncope, 2 years after that of dyspnea, and 1.5 to 2 years after that of congestive heart failure.[50] In general, without surgery, adults have an average mortality rate of 9% per year.[33] Valvular aortic stenosis is only one of various forms of left ventricular outflow obstruction; others include supravalvular aortic stenosis where the narrowing is distal to the aortic cusps, and subvalvular aortic stenosis with the obstruction below the aortic cusps.

B. PREVALENCE

The prevalence of valvular aortic stenosis varies with the population studied. The Helsinki Ageing Study[37] (discussed elsewhere in this paper) evaluated a random sample of patients between the ages of 75 and 86, and found that 5% had at least moderate valvular aortic stenosis while 3% had severe valvular aortic stenosis. When the latter population was divided into cohorts of smaller age range, the prevalence varied from 1% to 2% in patients aged 75 to 76 years to almost 6% in those who were 85 to 86 years old. In that study, the stenosis was considered moderate if the aortic valve area was ≤ 1.2 cm^2 but > 0.8 cm^2. It was considered severe if the valve area was ≤ 0.8 cm^2 and the velocity ratio ($V_{max}LVOT/V_{max}AV$) ≤ 0.35 or if the patient had undergone surgery during old age as a result of aortic valve stenosis. Furthermore, they also looked at patients between the ages of 55 and 71 and found no cases of aortic stenosis.[37]

Another study by Aronow and Kronzon[2] prospectively investigated 781 unselected patients between the ages of 62 and 100 (558 women and 223 men) in a long-term health care facility. They demonstrated the prevalence of mild (peak aortic flow velocity=1.6-2.5 m/s or peak gradient=10-25 mmHg), moderate (peak aortic flow velocity=2.6-3.5 m/s or peak gradient=26-49 mmHg), and severe (peak aortic flow velocity≥3.6 m/s or peak gradient≥50 mmHg) aortic stenosis to be 10%, 6%, and 2% respectively.

C. ETIOLOGY

Valvular aortic stenosis in adults is either congenital or acquired. When congenital, the aortic valve may be unicuspid or bicuspid and when acquired, may be tricuspid.[40] While the congenital form of the disease usually manifests anywhere from the neonatal period to late adulthood, acquired aortic stenosis is most prevalent in the elderly.[49] In a study which evaluated 188 patients over 40 years of age (26% women and 74% men) who had undergone aortic valve replacement because of severe stenosis and which consisted of only 29% of patients over age 65, Mautner et al. found that 62% of the patients had either a unicuspid or a bicuspid aortic valve while the remainder (38%) had a tricuspid valve.[40]

Acquired aortic stenosis can be divided into two types: valvular aortic stenosis due to degenerative changes, and valvular stenosis resulting from rheumatic diseases. Over the past few decades, there has been a decline in the prevalence of rheumatic heart disease. Thus the major cause of aortic stenosis has shifted from rheumatic to non rheumatic.[52]

Degenerative valvular aortic stenosis is characterized by focal fibrosis, lipidosis and calcification of the leaflets on the aortic side of the valve. The calcific lesions form a nodular ridge that is attached to the annulus, thereby

preventing the free motion of the annulocuspid junction. This process leads to cusp rigidity and the development of stenosis. At times, the cusps may become fixed in a semi-open position, leading to aortic regurgitation with or without concurrent aortic stenosis. Consequently, the valvular opening looks like a triangle whose sides bow inward.[25] Fusion of the commissures is very rare and when present, is only minimal.

On the other hand, aortic stenosis due to rheumatic fever is characterized by a valve that grossly looks "as though white candle wax had been poured over it". Furthermore, the cusp fibrosis is diffuse rather than focal and is associated with cusp rigidity and commissural fusion, both of which eventually lead to valvular stenosis. In general, the degree of aortic stenosis and the number of fused commissures are directly proportional. Usually cusp motion is further compromised by the formation of secondary calcification on the aortic and the ventricular sides of such valves.[25]

Even though the prevalence of degenerative valvular aortic stenosis clearly increases with age and aging brings changes to the valve leaflets, the absence of degenerative aortic stenosis (AS) in a large number of elderly individuals[37] makes it unlikely to be an inevitable consequence of aging. Rather, it appears to be a "tissue response to some initiating factor" as evidenced by Otto et al[45] in a study of 27 aortic valves. Taken at autopsy from adults between the

ages of 46 and 82, 6 of the valves were normal, 15 had mild macroscopic leaflet thickening, and 6 were from adults who had had clinical AS. Histological and immunohistochemical studies of the normal valves found scattered macrophages in the fibrosa and ventricularis, occasional muscle actin-positive cell in the ventricularis near the leaflet base, but no T lymphocytes. On the contrary, "early lesions" (evidenced by focal areas of thickening) were characterized by an inflammatory infiltrate made of non-foam cell and foam cell macrophages, occasional T cells, and few α-actin-positive cells. Stenotic valves had similar, although more advanced, lesions. They concluded that early degenerative AS is an active inflammatory process which presents some similarities (lipid deposition, macrophage and T-cell infiltration, and disruption of basement membrane) and some dissimilarities (prominent mineralization and few smooth muscle cells) to atherosclerosis.

This study raised questions concerning the regulation of the inflammatory process. O'Brien et al[43] investigated the presence of osteopontin, a protein known to be implicated in the regulation of normal as well as dystrophic calcification, in valvular aortic stenotic lesions. They evaluated 14 human aortic valves, ranging from morphologically normal to clinically stenotic, and concluded that osteopontin was present in both the early and late lesions of AS. They found highly statistically significant correlations between the amount of

osteopontin present and both the degree of calcification and the infiltration of macrophages. Lastly, they were able to demonstrate, by in situ hybridization, that a subset of lesion macrophages were actively producing osteopontin. O'Brien et al proposed that those results are compatible with the hypothesis that rather than being a degenerative and unmodifiable process, calcification of the aortic valve is, at least partly, an active process which requires the presence of inflammatory cells.

In light of the demonstrated presence of macrophages and T lymphocytes, two chronic inflammatory cells, in the lesions of AS and the fact that lipoprotein deposition is prominent in atherosclerosis, a known chronic inflammatory process, O'Brien et al[44] proposed that lipoprotein may also be present in aortic valve lesions. They looked at human aortic valvular tissue from autopsy specimens (n=15) and surgical specimens (n=3) from a total of 18 patients (tissue from those patients had been used in the study previously mentioned). Fifteen of the valves were either normal or mildly thickened (morphologically early disease). The remaining 3 valves were severely thickened and in those patients had shown clinical evidence of being severely obstructed. The results of the study were consistent with the hypothesis formulated. The accumulation of three apolipoproteins, namely apoB, apo(a), and apoE was demonstrated in AS

valvular lesions. Furthermore, prominent calcium deposition was observed in many areas of apolipoprotein accumulation.

The degree of calcification of the aortic valve varies for reasons that are unknown. Edwards[24] argues that, regardless of its etiology, AS is really the result of trauma to the leaflets. That trauma may be caused by either rheumatic disease, abnormal stress response from a bicuspid valve, or many years of normal function as in the case of a tricuspid valve. The latter is referred to as the "wear and tear" hypothesis. Functionally and histologically, the aortic valve is constructed so that mechanical stress is shared between the three leaflets and the sinuses of Valsalva.[16,19,56] Over the years, however, the continuous stress of opening and closing takes its toll and the valve is injured. This hypothesis is supported by the observation that patterns of calcification correspond to sites of increased mechanical stress[55,56] and that congenital bicuspid valves, which would be assumed to share stress less effectively, become diseased earlier and have more rapid progression of their stenosis.[4]

Other factors that contribute to the development of AS include diabetes and hypercholesterolemia,[21] but their role remains an area of dispute.[32] Deutscher et al.[21] looked at the relationship between these two factors and aortic stenosis in a retrospective study of 54 patients (between the ages of 40 and 87) with isolated AS who were undergoing cardiac catheterization; 461 patients

without AS who were having cardiac catheterization for other reasons were used as controls. They found odds ratios estimates greater than 2 for patients older than 50 but only approximately 1 for patients under the age of 50 (Table A) suggesting that there may be an age-dependent association between diabetes and "calcific aortic stenosis". The results held even when a subset of patients without coronary artery disease was evaluated. Hypercholesterolemia, defined as a cholesterol level ≥ 300 mg/100 ml, was also associated with aortic stenosis (Table B). On the other hand, in an attempt to analyze whether atherosclerotic risk factors such as systemic hypertension, hypercholesterolemia, smoking, and diabetes were associated with the presence of aortic stenosis, Hoagland et al[32] evaluated 105 patients, aged 50 or older, with presumed nonrheumatic aortic stenosis but no coronary artery disease, and compared them with 3 different control groups (Total=549 patients). When the control groups were combined, they found no statistically significant association between any of the risk factors and AS. The strongest association pertained to cigarette smoking (risk ratio=1.5) but the significance was marginal (p=0.06). All the above data, however, are based on small studies where the patients belonged to highly selected groups.[38]

In a study of unselected elderly people who participated in the Helsinki Ageing Study, a study conducted in the city of Helsinki to determine whether there was an association between aortic valve stenosis/calcification and risk

factors involved in calcium metabolism,[38] nine hundred people, born in 1904, 1909 and 1914 were originally sampled at random. By the time the survey started, 399 people did not participate due to either death, loss of contact, or unwillingness. In addition, 80 people born in 1920, 1925, 1930 and 1935 were randomly selected to join the study, but 4 of them declined. Of the 577 final subjects, complete ultrasound evaluation of the aortic valve was performed in 96 percent of them. They found age, hypertension, body mass index and high serum parathyroid hormone to be associated with valve calcification. Aside from age and hypertension, the traditional risk factors for atherosclerosis had no influence on the extent of aortic valve calcification. However, the concentrations of parathyroid hormone and ionized calcium were found to be associated with the degree of calcification and stenosis of the aortic valve, respectively. These results indicate an association between the metabolism of calcium and aortic valve calcification, but the mechanism of this association remains to be determined. The inverse relationship between body mass and aortic valve calcification was independent of age. Furthermore, it was found that gender, diabetes, serum lipids and smoking were unrelated to aortic valve calcification. We must point out that the above associations are statistical associations and do not imply direct causal relationships.[38]

Another study[40] which looked at factors that could predict the structure (i.e., the number of cusps present) of the stenotic aortic valve, and therefore the origin of the stenosis, found the following 4 factors to be significant: age, total serum cholesterol, body mass index and coronary artery disease. Patients with high values for or presence of 3 or all 4 factors (namely age>65 years, total serum chol>200 mg/dl, body mass index>29 kg/m^2 and coronary artery disease) had a low probability of having a congenitally malformed valve. On the other hand, patients with low values for or absence of 3 or all 4 factors (namely age≤65 years, total serum chol≤200 mg/dl, body mass index≤29 kg/m^2 and no coronary artery disease) had a high probability of having a stenotic valve whose origin was congenital. Furthermore, age was the strongest predictor and coronary artery disease the least significant.

In conclusion, the specific etiology of "degenerative" or "calcific" aortic stenosis has not been established categorically. Certainly, the old assumption that it is an inevitable consequence of old age has been challenged with recent evidences suggesting an inflammatory process.[43-45] Since inflammation is not an initiating event, but rather a response to some kind of insult, the question rises as to what might constitute an insult to the normal tricuspid aortic valve. The concept of "wear and tear", meaning repeated years of opening and closing causing trauma to the valve, is one that has been widely supported.[4,55-56]

However, since not all elderly people develop the disease, there must be more involved in the process. Factors such as diabetes, hypercholesterolemia, systemic hypertension, smoking and coronary artery disease may just be the other unknowns of the equation. Unfortunately, studies to date have not been successful at establishing definite causal relationships. More and larger studies are therefore needed.

D. PATHOPHYSIOLOGY

The obstruction to the left ventricular flow alters the hemodynamics in the left ventricle by creating a pressure overload. To maintain adequate cardiac output, the left ventricle's systolic pressure elevates and the ejection time increases. Progressively, the left ventricle hypertrophies without cavity enlargement ("concentric hypertrophy"), a compensatory mechanism whose effectiveness varies with the adequacy of the thickening. Both the interventricular septum and the posterior wall have a normal thickness of up to 12 mm but in one patient with AS, they went up to 14 mm and 19 mm, respectively.[46] Therefore, left ventricular (LV) concentric hypertrophy represents the major adaptive mechanism to valvular aortic stenosis.[27] However, this compensation results in a reduced diastolic compliance and an

increased oxygen consumption, both of which eventually lead to congestive heart failure, myocardial ischemia and angina pectoris, all well known symptoms of valvular aortic stenosis. Although patients with severe aortic stenosis usually show "marked left ventricular hypertrophy and strain", the evidence of "borderline left ventricular hypertrophy" does not exclude the diagnosis. Older patients need a less severe stenosis for decompensation to take place. Consequently, the same degree of stenosis can be considered moderate in a young patient and severe in an elderly patient.[54] It is worth mentioning that not all patients with AS express increased transvalvular gradient. In fact, some patients present with the clinical syndrome of severe AS, a low mean gradient, and left ventricular dysfunction.[20]

It has been documented that the progression of severity of aortic stenosis and an increase in left ventricular wall thickness usually coexist. However, investigators[27] have recently reported two cases of patients with severe aortic stenosis but normal thickness of the left ventricular wall. In one patient (patient 1), an increase in the severity of the stenosis was seen with an increase in left ventricular dimensions, and a reduction in the thickness of the wall in addition to systolic function (Figure 1).[27] Also present, were symptoms of heart failure which worsened over time. Echocardiographic exams of the other patient (patient 2) confirmed these observations. Usually, in patients with aortic

stenosis, symptoms of congestive heart failure are indicative of poor left ventricular systolic function. However, heart failure is also seen in patients with intact systolic function. These cases have diastolic dysfunction of the left ventricle.[22] Recently, studies have shown that differences in the geometry of the left ventricle are directly related to ventricular performance. For example, patients with normal systolic function of the left ventricle have smaller left ventricle with thick walls while those with left ventricular systolic dysfunction have larger left ventricle.[28] It remains to be demonstrated whether the thinning of the left ventricular wall is the late stage in the remodeling of the ventricle in patients with AS, or a totally different response to a chronic state of pressure overload. Nonetheless, Faggiano et al.[27] believe that the changes in both the geometry and the function of the left ventricle seen in these patients may be the results of " excessive pressure afterload" as well as "structural abnormalities due to long-term cardiac hypertrophy".[35] These patients being males is a significant fact since a recent study published by Carroll et al.[11] showed sex-related differences in the resulted function of the left ventricle in patients with AS.

The classical symptoms of valvular aortic stenosis are angina pectoris, dyspnea, and syncope with survival periods of 5, 2, and 3-4 years, respectively. Sudden death occurs in 3%-5% of asymptomatic patients and in 15%-20% of symptomatic patients. The reason asymptomatic patients may suddenly die is

because the normal opening area of the aortic valve, which is 3 to 4 cm^2, may decrease, without symptoms, to 0.75 cm^2.[5] Angina and syncope are more often seen in younger patients, while older patients usually present with heart failure.[54]

Valvular aortic stenosis is usually associated with aortic regurgitation which gives rise to a murmur. A third heart sound or S_3 gallop in patients with valvular disease is usually seen as a sign of heart failure.[30] It has also been associated with other problems such as elevated atrial pressure[36] and abnormal ventricular function.[1] The sound depends on three factors: atrial pressure, early diastolic filling rate, and ventricular compliance. According to Folland et al,[29] a third heart sound is not as prevalent in aortic stenosis patients (11%) as it is in patients with mitral regurgitation (46%) or aortic regurgitation (28%). In aortic stenosis patients with a third heart sound, the ejection fraction of the left ventricle was found to be much lower ($p<0.001$) and the pulmonary wedge pressure was higher ($p<0.001$). These associations were either less significant (as in the case of ejection fraction) or nonexistent (as in the case of pulmonary wedge pressure) in patients with mitral regurgitation and third heart sounds. Therefore, although S_3 are uncommon in patients with aortic stenosis, its presence is a "strong indicator of left ventricular failure".[29]

E. DIAGNOSIS

1. Bedside

As already mentioned, angina pectoris, dyspnea, and syncope are the classical symptoms of aortic stenosis. In the elderly, however, the disease can be without clinical signs or at least, until late in its course.[12] Even in the presence of a murmur characteristic of AS, a patient may remain asymptomatic. Besides these cardiac symptoms, patients also experience non-cardiac symptoms such as fatigue. In a study of 41 patients, dyspnea was reported as the major cardiac symptom while fatigue constituted the major non-cardiac symptom.[12] The clinical diagnosis of AS in elderly patients is difficult since this population has a high prevalence of the degenerative type of AS and the changes in the vascular system due to old age alter the main clinical signs of the disease. Because the systolic blood pressure and the pulse pressure are generally higher in the elderly, they can not be used as reliable diagnostic criteria.[39] Furthermore, the systolic murmur heard in AS is less intense than in younger patients and, therefore, can be mistaken for a murmur due to aortic sclerosis or mitral regurgitation.[7] AS patients experience a fall in cardiac output, a condition which makes the murmur of AS softer or eliminates it altogether. Consequently, low cardiac output presented with pulmonary edema should alert the physician to the possibility of

"occult AS".[41] The clinical diagnosis of AS unfortunately has many flaws. One study reported that out of 8 patients with AS, only 3 were diagnosed clinically over a period of six months. It is very important that the diagnosis of AS be ruled out in patients with cardiac failure, since some drugs such as angiotensin-converting enzymes (ACE) inhibitors, while beneficial in the treatment of cardiac failure, are contraindicated when AS is present.[12] Thus, other methods of diagnosis are necessary.

2. Non-Invasive

Echocardiographic methods, which are tests that use ultrasound to examine the heart and report information as echoes (reflected sonic waves), have totally revolutionized cardiological investigations. Ultrasound has a frequency above that detected by humans (>20,000 cycles/sec). In medicine, frequencies greater than 1,000,000 cycles/sec are used and no biological side effects have been demonstrated so far. However, its efficacy is limited since it cannot penetrate lungs and bones. The accuracy of ultrasound interpretation is very much dependent upon the quality of the examination.[26] There exists three modes of echocardiography: the A-mode (A for amplitude), the B-mode (B for brightness) and the M-mode (M for motion). An M-mode allows recording of amplitude and rate of motion, but it gives a one-dimensional view of the heart.

Complementing the M-mode, however, is a two-dimensional echocardiographic technique called 2-D which permits a pie-shaped slice of the heart to be studied (B). M-mode and 2-D echocardiographic techniques are used to make the diagnosis of calcified or thickened aortic cusps or root. In the Helsinki Ageing Study, mentioned previously in this paper, calcification of the aortic valve was diagnosed by M-mode and 2-D echocardiography in 53% of patients between 55 and 86 years of age.[37] M-mode and 2-D are also used to measure chamber dimensions, left ventricular end-diastolic and end-systolic volumes, LV ejection fraction, and to determine global and local left ventricular wall motion.[3]

While the M-mode and the 2-D allow a qualitative diagnosis of aortic stenosis, they are not effective at providing quantitative data. For that, investigators turn to Doppler echocardiography. Three forms of Doppler interrogation are in use: pulse-wave (PW), color-flow (CF), and continuous wave (CW) Doppler. Of the three, CW is the only one that allows accurate measurement of very high frequencies, well above those encountered in patients with AS.[26] It is now the method of choice for getting hemodynamic information. It is used to measure blood flow and it can also measure the pressure gradient across the aortic valve, using a modified version of the Bernoulli equation. Furthermore, the area of a valve can be calculated, using the "continuity equation", and combining Doppler principles for measuring blood flow and

pressure gradient. Consequently, Doppler echocardiography allows the differentiation between aortic stenosis and aortic sclerosis, a distinction which is not possible with M-mode and 2-D.[12] Echocardiography can also determine the degree of severity of the stenosis. Severe aortic stenosis is usually diagnosed when the aortic valve area is < 0.7 cm^2, or if the peak pressure gradient across the valve is ≥ than 50 mmHg.[3] However, one cannot always rely on the transvalvular gradients since some patients with severe AS and left ventricular dysfunction have been known to present with low transvalvular gradients. One study by deFilippi et al.[20] used dobutamine echocardiography to try to overcome this diagnostic problem. It was found that dobutamine echo could determine three subsets of hemodynamics in patients with severe AS, low transvalvular gradients and LV dysfunction. Patients with fixed AS showed increased cardiac output and gradient across the valve but aortic valve area remained the same. Patients with relative AS had a constant gradient but an increased valve area. Lastly, patients without contractile reserve could not increase their cardiac output with dobutamine and were said to have an indeterminate AS. Therefore, dobutamine allows the differentiation of patients whose LV dysfunction is a consequence of critical AS from those whose dysfunction is due to an underlying cardiomyopathy, thereby identifying patients who are likely to benefit from aortic valve replacement. In addition, this

study showed that valve resistance is flow-dependent in patients with fixed AS, whereas valve area is flow-dependent in those with relative AS.[20]

3. Invasive

While non-invasive methods of diagnosing aortic stenosis are fairly recent, invasive methods using cardiac catheterization go further back in the history of AS and are still very much in use today. There have been studies done comparing the efficacy of non-invasive and invasive diagnostic techniques. Shah and Graham[53] reported a greater than 95% agreement between Doppler echocardiography and cardiac catheterization when used to quantify the severity of AS. When the peak jet velocity was ≥ 4.5 m/s in a patient, he/she was considered to have severe AS. If Doppler echocardiography shows peak jet velocity between 3.6 and 4.4 m/s in older patients who have cardiac symptoms due to AS, they should undergo cardiac catheterization. Older patients with a peak jet velocity anywhere from 3.0 to 3.5 m/s and a less than 50% left ventricular ejection fraction, may have severe AS and should be given a cardiac catheterization. Lastly, older patients who have a peak jet velocity between 3.0 and 3.5 m/s but whose LV ejection is > 50%, should be subjected to cardiac catheterization providing they have symptoms indicative of AS.[53] Cardiac

catheterization is therefore, sometimes, used as a confirmatory technique after Doppler echocardiography has been used as the primary diagnostic tool.

While Doppler echocardiography uses the continuity equation to measure aortic valve area, invasive techniques use what is called the Gorlin equation to the same end.[31] Gorlin valve area has been seen to change in in vitro models using fixed orifice areas.[10,51] This has been explained by the fact that the Gorlin equation uses a discharge coefficient which is susceptible to volume flow-mediated variability.[51] There exists a linear relationship between the transvalvular volume flow rate and the valve area calculated by this equation.[9] The continuity equation and the Gorlin equation are based on similar hydrodynamic principles[31] and recently, it has been demonstrated that the continuity equation also is dependent on transvalvular volume flow rate in valvular AS.[9]

F. TIMING OF SURGERY

Surgery is recommended for patients with symptoms of severe AS. Replacement of the aortic valve may be beneficial even to patients with severe left ventricular dysfunction and symptoms of advanced heart failure.[59] The risks and benefits of surgery must be carefully considered before proceeding,

however. In a fairly young patient, this may not be such a complicated issue, because the life expectancy of the patient usually overrides everything else. It is a very different matter when the patient is an 87-year-old woman, as in the case reported twice in the New England Journal of Medicine under the titles "Too old for what"[54] and "You're never too old".[60] This particular patient had "severe aortic stenosis, three vessel coronary artery disease, depressed left ventricular function, and moderately severe heart failure". The life expectancy of this woman, who happened to be healthy and vigorous, was 5 years. On the other hand, that of patients with AS and congestive heart failure together is ≤ 2 years[60]. From these numbers, it appears that she clearly could benefit from surgery. However, one needs to keep in mind that aside from the benefits, valve replacement in the elderly is associated with high mortality and morbidity rates.[23] This woman's operative risk was 8 to 10 percent or even higher, but her doctor felt that the risk was worth taking because surgery would improve her life tremendously. After all, in patients her age, the primary aim of surgery is to improve the quality of life rather than prolonging it.[54]

Seven studies of AS patients, between 1934 and 1960, whose mean age was 61, showed a life expectancy of 2 years after onset of dyspnea, giving a mortality rate of 49% per year.[50] More recent studies of 45 patients with a mean age of 59, aortic stenosis, and congestive heart failure, showed a mortality rate of

54% per year. These patients either declined surgery or the risks were considered to be much too high.[15] In contrast, four studies of 157 octogenarians (mean age, 82) who had successful aortic valve replacement[23] and three studies of 51 octogenarians (mean age, 82) who survived aortic valve replacement and coronary bypass surgery[23] demonstrated a mortality rate of 0.4% per year.[60] In cases of severe AS, it seems that "you're never too old". Even for the older patients, aortic valve replacement may provide substantial benefits.[60]

Doppler echocardiography has allowed physicians to follow patients so that the optimal time for surgical intervention can be determined before damages to the left ventricle become irreversible or before cardiac events of any significance have occurred.[6] We must mention that a symptomless case of AS does not exclude the possibility of surgery. In fact, progressive valvular dysfunction and dilation, even in the absence of symptoms, may indicate the need for surgery.[6]

G. RATE OF PROGRESSION OF THE DISEASE

Aortic stenosis is a slowly progressive disease. Therefore, for years, there may be no or only minimal symptoms. As the disease worsens, many hemodynamic and structural changes take place such as: progressive increase in

transvalvular gradients and hypertrophy of the left ventricle, resulting in decreased systolic and diastolic functions along with ventricular dilation.[6] Also seen in the late stage of AS are: abnormal ventricular filling, mitral regurgitation and symptoms of heart failure, syncope or angina. Brener et al.[6] did serial Doppler echoes on 394 consecutive patients with valvular AS at baseline and after a period of 37 ± 16 months and reported that increasing wall thickness is an adaptive mechanism that allows the ventricle to eject blood against an increased gradient, created by the stenosis, by building up a higher intracavitary pressure. This increase in wall thickness permits preservation of ventricular size. In others, however, mitral regurgitation ensues due to loss of forward output when the ventricle dilates.[6] The reasons why these variations exist are not well understood. There is a limit to the adaptive nature of left ventricular wall hypertrophy. In fact, it may reach a point where the systolic wall stress is so high that it reduces the ejection fraction. The defect in fiber shortening is not a result of "intrinsic muscle dysfunction", but rather that of a "mismatch" between the amount of thickening and the "increased afterload". Furthermore, Brener et al.[6] found no correlation between systolic dysfunction and AS progression though they found increases in mitral regurgitation and systolic dysfunction to be very well correlated. This finding may be explained by the possibility of systolic

dysfunction being masked by the increasing mitral regurgitation which decreases the fluid volume of the left ventricle.

On the average, aortic stenosis, measured by aortic valve area, progresses predictably at a rate of about 0.14 cm^2 per year.[6] Peter et al.[47] analyzed the rate of progression of aortic valve gradient and of fractional shortening-velocity ratio in 49 patients and reported a median rate of progression of 7.2 mmHg per year. They also found that rapid progression (≥10 mmHg/yr) was more prevalent in AS patients with coronary artery disease. Moreover, aortic regurgitation, documented at the time of the first catheterization, was associated with greater rates of progression. Even though there is strong statistical correlation between rapid rate of progression and valve calcification, valve regurgitation and coronary artery disease, most of the variability in the rate of progression remains unexplained, as shown by the low correlation coefficients (0.3-0.4).[17]

One study,[35] which looked at congenital aortic valve stenosis, reported that patients who presented with mild stenosis had a much better prognosis than those with a moderate stenosis. Although congenital AS is mostly mild at presentation, fewer than 20% of the patients will have mild stenosis 30 years later. Therefore, progression does occur with time in most patients.

H. CONCLUSION

At this point, it remains a problem to predict the likelihood or rate of progression of AS in patients who present with mild or moderate disease. It is, however, a problem which may have irreversible consequences for patients if the risks are underestimated. Therefore, it is a matter which requires consideration, and Doppler echocardiography may just be the tool that holds the answer to this important question.

III. STUDY QUESTIONS

What is the rate of progression of AS in our veteran population? What are the factors which can help predict the rate of progression of AS?

IV. METHODS

A. PATIENT POPULATION

A group of 109 patients were selected from Dr. Ira Cohen's database at the West Haven Veteran Medical Center. They were all patients with varying degrees of aortic stenosis who had had at least one echocardiogram within the

previous 18 months. They ranged in age from 44 to 97 with an average of 71 (median=72, mode=73). Patients were reviewed both retrospectively and prospectively from the time of ascertainment. Data was collected from their echo charts, their medical charts, and their computerized lab values.

Two groups of patients were analyzed. To evaluate the progression of the disease, the first group included only those patients who had more than one measure of the area of the aortic valve (AVA). Of the 109 patients originally identified, only 32 fit that criterion. Their ages ranged from 58 to 87 years and averaged 74.25 (median=75, mode=77).

The second group included patients based on their peak aortoventricular gradient (pk AV gd), and only those who had more than one value for that parameter qualified. Of the 109 patients, 69 met that criterion and their ages ranged from 51 to 86 with an average of 72 (median=73, mode=77).

B. DATA ANALYSIS

1. AVA Group

For each of the 32 patients in that group, we graphed the area of the aortic valve and subgrouped them based on whether they had a decrease (defined as "any decrease"), or an increase or no change in the AVA. We used an unpaired

t-test to determine whether the duration of observation was comparable in those two subgroups. Each subgroup was then characterized according to the following risk factors: age, history of hypertension (HTN), smoking, cholesterol level (chol) > 200. HDL < 29, triglyceride (trig) > 160, non insulin-dependent diabetes mellitus (NIDDM), insulin-dependent diabetes mellitus (IDDM), blood urea nitrogen (BUN), and creatinine (Cr) > 2.

For each of the above 9 risk factors, the patients with decrease in the AVA were further divided according to the presence or the absence of that factor. The mean AVA decrease and one standard deviation (1 SD) were calculated. A paired t-test was used on each group of patients with a particular risk factor and p values determined to establish any significance. In addition, those patients were also divided according to the number of risk factors present and again, mean AVA decreases were calculated, paired t-tests were used and p values were determined. Furthermore, looking at all patients with AVA decrease, correlation coefficients were calculated for each individual risk factor and for the number of risk factors present.

Lastly, we ran a multiple regression analysis on all the thirty-two patients in order to determine the collective effect of the nine risk factors studied.

2. Peak AV Gradient Group

Considering the 69 patients in that group, the same analyses were carried out as for the AVA group, with the exception of the multiple regression analysis. The other difference was that patients were subgrouped based on whether they had an increase (defined as "any increase"), or a decrease or no change in the peak AV gradient (pk AV gd).

V. RESULTS

A. AVA GROUP

Of the 32 patients included in this group, 21 (65.6%) were found to have a decrease in the AVA, indicating progression of the stenosis (subgroup A), while the remaining 11 had either an increase or no change (subgroup B). The average duration of observation was 15 months ± 6 (1 SD) for the former subgroup and 16 months ± 6 (1 SD) for the latter.

Patients in subgroup A had an average age of 74 (range=62-87). In addition, 67% were hypertensive, 43% smoke, 33% had a cholesterol level > 200, 10% had an HDL < 28, 29% had a triglyceride level > 160, 10% had NIDDM, 5% had IDDM, 14% had BUN > 40, and another 14% had a creatinine > 2 (Table 1). On the other hand, subgroup B showed the following characteristics : average

age of 74.5 (range=58-83), 82% with a history of HTN, 73% positive for smoking, 64% with cholesterol > 200, 0% with HDL < 28, 9% with triglyceride > 160, 9% with NIDDM, 0% with IDDM, 18% with BUN > 40, and 18% with creatinine > 2 (Table 1).

Patients in subgroup A had an overall mean AVA decrease of 0.35 cm^2 ± 0.17 (1 SD), equivalent to 0.35 cm^2/year ± 0.22 (1 SD), while those in subgroup B had an overall mean AVA increase of 0.34 cm^2 ± 0.33 (1 SD). The presence of HTN, smoking, chol > 200, trig > 160 and NIDDM was associated with a greater mean AVA decrease (Table 2).

The two-tailed t values were all very small and the p values not significant (Table 3). Except for HTN which had a correlation coefficient of 0.51 (although still under 0.6 which is usually considered significant), all the other risk factors studied had very low coefficients, ranging from -0.27 to +0.26 (Table 3).

Results were similar when patients were grouped according to the number of risk factors present, the most being 5 and the least 0. All two-tailed t values were very small, leading to insignificant p values, and correlation coefficients ranged from -0.53 to +0.50. Those two extreme coefficients correspond to the absence of all risk factors and the presence of 2 risk factors, respectively (Table 4). Lastly, patients with 2 risk factors seemed to have the greatest mean AVA decrease (Table 9).

The multiple regression analysis yielded a collective correlation coefficient of 0.363 when all nine factors were studied simultaneously, for a corresponding insignificant p value of 0.887. When the effect of each risk factor was investigated separately, a triglyceride level > 160 was found to have the greatest correlation coefficient (0.246). However, the corresponding p value was not significant (p=0.174). Moreover, the total number of risk factors appeared to have an inverse correlation with disease progression (Coefficient=-0.019).

B. PEAK AV GRADIENT GROUP

That group comprised 69 patients, 58 of whom were found to have an increase in the peak aortoventricular gradient (subgroup C) while the remaining 11 had either a decrease or no change (subgroup D). The former had an average study time of 4.6 years ± 2 (1 SD) and the latter of 2.7 years ± 1.9 (1 SD).

The mean age of patients in subgroup C was 72 (range=51-86) compared to 74 (range=59-83) in subgroup D. Furthermore, subgroup C was characterized by 71% HTN, 52% smoking, 48% chol > 200, 7% HDL < 28, 21% trig > 160, 10% NIDDM, 7% IDDM, 14% BUN > 40, and 14% Cr > 2. The percentages for subgroup D were 72%, 45%, 55%, 0%, 55%, 9%, 0%, 9%, and 27% respectively (Table 5).

The overall average increase in the pk AV gd was 22 mmHg ± 2.39 (1 SD) (6 mmHg/year ± 5.5 [1 SD]) in subgroup C but the average decrease was only 5 mmHg ± 1.90 (1 SD) in subgroup D. A history of HTN and the presence of NIDDM were the only 2 factors associated with a higher pk AV gd increase when compared with the groups in which they were absent (Table 6).

Similar to the analysis of the AVA group, the two-tailed t values calculated for each risk factor taken separately were very small and the corresponding p values very high (p=NS in all groups). In addition, the correlation coefficients were also very low, ranging from -0.17 to +0.19 (Table 7).

Finally, the analysis of groups based on the number of risk factors present again yielded results similar to those of the AVA. In that group, the most risk factors present simultaneously in any one patient was 6 and the least 0. The two-tailed t values were extremely small and the p values failed to show significance. The correlation coefficients also were low, with a very narrow range (from -0.09 to +0.12) (Table 8). Furthermore, the presence of 6 risk factors appeared to be associated with the largest mean pk AV gd increase as shown in table 10.

VI. DISCUSSION

A. MAJOR FINDINGS

This study found a mean rate of progression of aortic stenosis of 0.35 cm^2/year ± 0.22 (1 SD). Twenty one out of thirty two patients experienced progression during the mean 15 month ± 6 (1 SD) observation period. The greatest average AVA decrease, 0.48 cm^2/year ± 0.21 (1 SD), was associated with the simultaneous presence of 2 risk factors (any 2 factors).

We found a mean peak AV gradient increase of 6 mmHg/year ± 5.5 (1 SD). Over the average course of 4.6 years ± 2 (1 SD), increase in transvalvular gradient was observed in fifty eight of the sixty nine patients in that group. Lastly, the greatest mean increase, 8.1 mmHg/year ± 7.7 (1 SD), was seen in association with 4 risk factors simultaneously present.

B. AVA GROUP

1. Overall Results

Twenty one (subgroup A) out of the 32 patients in that group were found to have a progression of their stenosis, which averaged 0.35 cm^2± 0.17 (1 SD) over a mean 15 month period ± 6 (1 SD) (0.35 cm^2/year ± 0.22 [1 SD]). All the 9 risk factors studied were present in subgroup A as opposed to 7 (HDL<29 and IDDM were absent)) in the remaining 11 patients (subgroup B). Only HDL < 29, trig > 160, NIDDM and IDDM were present in a greater percentage of patients in

the former subgroup, compared to the latter (Table 1). Within subgroup A, the presence of a history of HTN, smoking, Chol > 200, trig > 160, NIDDM, and any 2 risk factors were found to be associated with a greater progression of AS as measured by the average decrease in the AVA (Tables 2 and 9). Finally, using two-tailed paired t-tests and correlation coefficients, none of the 9 factors was found to be significantly correlated with disease progression (Table 3). Neither were the number of risk factors present simultaneously in any given patient (Table 4).

2. Individual Risk Factors

a. *History of HTN*

This risk factor was not found to be significantly associated with disease progression, though with a correlation coefficient of 0.51, it had the best association (Table 3). Hoagland et al.[32] also demonstrated this lack of significance. However, these results are not consistent with those of the Helsinki Ageing Study (discussed in the introduction of this paper) which showed HTN to be significantly associated with AS.[38] It must be emphasized that both our study and the one by Hoagland et al. are small studies (32 and 105 patients respectively) based on selected groups, while the Helsinki study was larger (577 patients) and comprised unselected cohorts of elderly people.

b. *Smoking*

Smoking was second only to HTN as far as the strength of its correlation with AS progression (coefficient=0.26). However, that correlation was not significant. (Table 3). The absence of statistical significance was also demonstrated by Hoagland et al.,[32] as well as the Helsinki Ageing Study.[38]

c. *Serum Lipids*

We found no statistical significance in the association between any of the lipids and AS progression (Table 3). These results are compatible with those reported by Hoagland et al.[32] and by Lindroos in the Helsinki Ageing Study.[38] However, they differ from those of Deutscher et al. who found an age-dependent association between hypercholesterolemia, defined as a chol ≥ 300 mg/ml, and "calcific aortic stenosis".[21] In this study, we used 200 as the cut-off value instead of 300, a choice which should increase the strength or the magnitude of the association rather than the reverse. The Deutscher et al. study was smaller than the ones mentioned above, with only 54 patients and included very selected patients.

d. *Diabetes*

Statistically, neither NIDDM nor IDDM was found to be significantly associated with AS progression (Table 3). Hoagland et al.[32] and Lindroos[38] found similar results. On the other hand, in the same study that

looked at hypercholesterolemia, Deutscher et al. found diabetes to be associated with AS in an age-dependent fashion.[21] However, as we have mentioned above, that study was very small and selective (54 patients with AS), especially compared to the Helsinki study (577 unselected patients).[38]

C. PEAK AV GRADIENT GROUP

1. Overall Results

Of the 69 patients in that group, 58 (84%) (subgroup C) experienced increase in the peak gradient across their aortic valve, the mean being 22 mmHg ± 2.39 (1 SD) over the course of an average of 4.6 years ± 2 (1 SD) (6 mmHg/year ± 5.5 [1 SD]). As with the AVA group, all 9 risk factors were present in subgroup C, compared with 7 (HDL<29 and IDDM absent) in subgroup D (the 11 patients who did not experience increase). A greater percentage of patients in subgroup C had the following risk factors: smoking, HDL < 29, NIDDM, IDDM and BUN > 40 (Table 5). Within subgroup C, only a history of HTN and NIDDM were found to be associated with a greater average increase in the gradient (Table 6). So were the presence of 2 and 4 risk factors simultaneously (Only one patient in that group had 6 risk factors and that value, although the largest, is therefore not reliable) (Table 10). Lastly, none of the 9 risk factors was significantly correlated

with pk AV gd increase, as assessed by two-tailed paired t-tests and correlation coefficients (Table 7). That was also true of the number of risk factors present simultaneously in a patient (Table 8).

D. RATE OF PROGRESSION

Based on measurements of the aortic valve area, this study found an average rate of AS progression of 0.35 cm^2/year ± 0.22 (1 SD), a rate more than twice as fast as the 0.14 cm^2/year quoted in the literature.[6] Based on the gradient across the valve, it was found to be 6 mmHg/year ± 5.5 (1 SD), compared to 7.2 mmHg/year and 8.3 mmHg/year as reported by Peter et al.[47] and Brener et al.,[6] respectively.

While the progressive nature of aortic stenosis has been consistently demonstrated among patients, the rate at which it progresses remains highly variable between patients. Factors that have been associated with a greater rate of progression (i.e., >0.15 cm^2/year) are: degenerative-calcific AS,[13,57] initial mild degree of AS,[6,14,42] presence and extent of valve calcification,[18] aortic regurgitation (AR)[18] (those two being specifically associated with a greater pressure gradient rate of increase), mitral regurgitation (MR),[6] significantly

reduced cardiac output,[57] progressive left ventricular hypertrophy (LVH),[6] and symptomatic or angiographic evidence of coronary artery disease (CAD).[17,47]

All of the 21 patients who experienced disease progression had "degenerative-calcific" AS since none of them was noted to have an abnormal aortic valve structure on echocardiography. Only 3 of the 21 had mild AS at the beginning of the observation period (p=NS); the others had either moderate (16 patients) or severe (2 patients) AS. Valve calcification, however, was present in all of them in either a moderate (12 patients) or a severe (9 patients) form. Sixteen of the 21 patients had aortic regurgitation (10 mild, 3 moderate, and 3 severe) (p=NS), while 11 of them had mitral regurgitation (7 mild and 4 moderate) (p=NS). Cardiac output was not calculated directly. However, since progressive impairment of systolic function can lead to reduction in cardiac output (CO), we can look at systolic function in lieu of CO. Among the 21 patients with progression, only 6 had impaired systolic function (p=NS) while 14 showed progressive LVH (p=NS). Coronary artery disease was not looked at in this study.

Of those 8 factors reported in the literature as having an association with a greater rate of AS progression, 7 were looked at in this study. Two of them ("degenerative-calcific stenosis" and AV calcification) were present in all 21 patients with AS progression. Another three (MR, progressive LVH, and AR)

were present in a greater number of patients. The remaining two (initial mild AS and impaired LV function) were not found to be more prevalent in this group. All p values failed to show any statistical significance.

On the other hand, since aortic valve calcification and aortic regurgitation (AR) have been found to be associated with a greater increase in peak AV gradient across the valve,[18] we looked at the prevalence of those two factors in the peak AV gradient group. Valve calcification was present in all 58 patients in that group (5 mild, 25 moderate, and 28 severe), while AR was observed in 30 of them (18 mild, 9 moderate, and 3 severe) (p=NS). Despite these high prevalences, the average peak AV gradient increase in this study was only 6 mmHg/year ± 5.5 (1 SD), compared to 7.2 mmHg[47] and 8.3 mmHg[6] previously reported. This value was also much lower than the one quoted by Davies et al. who found the presence and extent of valve calcification to be associated with a greater rate of increase in pressure gradient (9.7 mmHg/year vs 4.4 mmHg/year).[18]

E. LIMITATIONS

1. Reliability of measuring valve area and gradient

The valve area is a calculated number. It is calculated by the continuity equation when Doppler echocardiography is used, and by the Gorlin equation when invasive techniques are used. However, both of those equations are dependent on the transvalvular volume flow rate. Therefore, valve area measurements may be difficult to interpret in the setting of reduced transvalvular flow associated with left ventricular dysfunction.[9]

Of the 21 patients in the subgroup with AVA decrease, 6 had LV dysfunction. Analysis of only those with preserved LV function, however, did not yield different results. The average AVA decrease was 0.35 cm^2/year ± 0.18 (1 SD), compared to the 0.35 cm^2/year ± 0.22 (1 SD). Furthermore, the 6 patients with LV dysfunction experienced a negligibly lesser decrease (0.34 cm^2/year±0.32 [1 SD]) (p=NS).

The gradient across the valve is dependent upon two factors: the area of the valve and the ventricular function. In other words, adequate flow is needed, together with a reduced aortic valve area in order to establish a gradient. Thus, even in the presence of a stenotic aortic valve, the gradient may not be comparatively elevated if ventricular function is reduced.

Of the 58 patients who experienced a decrease in their peak AV gradient, 10 had ventricular dysfunction. However, they constitute a small percentage of the whole group (17%) and they should not affect the study results overall.

Therefore, the 6 mmHg/year ± 5.5 (1 SD) mean increase should be close to the actual increase. When the analysis was repeated for the 48 patients with preserved LV function, the average peak AV gradient increase was found to be 6.7 mmHg/year ± 5.9 (1 SD), compared to 3.9 mmHg/year ± 2.1 (1 SD) for the 10 patients with LV dysfunction (p=NS).

2. Sample size

Although we started out with a sample of 109 patients, we were able to include only thirty-two in the analysis which looked at decreases in the area under the aortic valve as indicators of disease progression. This limitation is a direct result of the largely retrospective nature of our study, since we could not make sure that the proper measurements were taken during the echocardiograms or that the specific information was asked during history-taking.

The statistical power of our sample was, therefore, presumed low at the onset. Indeed, it was calculated for each of the tests performed and found consistently to be very low. The small sample was even more inappropriate for the multiple regression analysis, especially since we looked at a total of nine factors. Generally, the more factors under consideration, the more patients needed in order to be able to dissociate the effects of one from another. In fact,

our sample is so small that many would even argue against the use of such analysis. Consequently, it is not surprising that our analyses yielded non significant results.

In light of this limitation, we can not conclude that the nine factors investigated in this study are not statistically significantly associated with aortic stenosis progression. They did not seem to be, based on our results. However, even if they had appeared to be, our sample has such low statistical power, that we would have had to question the validity of such results. Larger studies are therefore needed.

TABLE A

Effect of diabetes upon risk of aortic stenosis, according to age group

Age	Aortic stenosis cases: Total no. of patients	Aortic stenosis cases: No. with diabetes	Controls: Total no. of patients	Controls: No. with diabetes	Odds ratio	p value
<50	8	1(12.5%)	102	12(11.8%)	1.07	NS*
50-59	20	7(35.0%)	256	37(14.4%)	3.20	<0.05*
60	25	7(28.0%)	103	16(15.5%)	2.11	NS*
Age groups 50-59 and 60 combined	45	14(31.1%)	359	53(14.8%)	2.62† (1.17-5.53)§	<0.01

* Statistical significance of difference from unity based on Mantel-Haenszel chi-square statistic for single stratum.

† Mantel-Haenszel age adjusted summary odds ratio.
Mantel-Haenszel chi-square statistic for testing overall association: 7.514

§ 95% confidence interval.

Adapted from Deutscher et al.[21]

TABLE B

Effect of hypercholesterolemia upon risk of aortic stenosis, according to age group

	Aortic stenosis cases		Controls			
Age	Total no. of patients	No. with cholesterol 300 mg	Total no. of patients	No. with cholesterol 300 mg	Odds ratio	p value
<50	7	0	102	17(16.7%)	.....	NS*
50-59	19	6(31.6%)	253	29(11.5%)	3.61	<0.02*
60	25	6(24.0%)	98	12(12.2%)	2.26	NS*
Age groups 50-59 and 60 combined	44	12(27.3%)	351	41(11.7%)	2.75† (1.20-6.39)§	<0.01

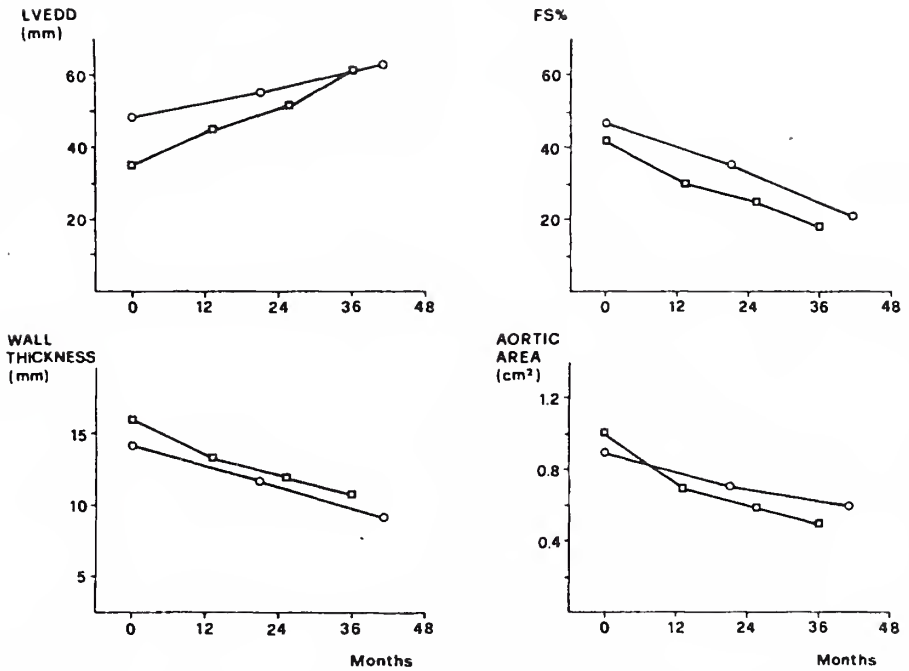
* Statistical significance of difference from unity based on Mantel-Haenszel chi-square statistic for single stratum

† Mantel-Haenszel age adjusted summary odds ratio.
Mantel-Haenszel chi-square statistic for testing overall association: 7.510.

§ 95% confidence interval.

Adapted from Deutscher et al.[21]

FIGURE 1



Changes of echocardiographic parameters during follow-up in two patients with severe aortic stenosis but normal left ventricular wall thickness. *Top left*: left ventricular end-diastolic diameter (LVEDD), *top right*: left ventricular fractional shortening (FS), *bottom left*: mean wall thickness at end diastole, *bottom right*: aortic area calculated according to the continuity equation by Doppler. Patient 1 is indicated by open squares and patient 2 by open circles.

Adapted from Faggiano et al.[27]

TABLE 1

Comparison between patients with decrease in AVA and those without decrease, according to risk factors

	Subgroup A [1] (21 patients) # (%)	Subgroup B [2] (11 patients) # (%)	t values	p values
Risk factors				
HIST. OF HTN	14 (67)	9 (82)	0.409	NS
SMOKING	9 (43)	8 (73)	0.231	NS
CHOL>200	7 (33)	7 (64)	0.4	NS
HDL<29	2 (9.5)	0 (0)	§	§
TRIG>160	6 (29)	1 (9)	§	§
NIDDM	2 (9.5)	1 (9)	§	§
IDDM	1 (5)	0 (0)	§	§
BUN>40	3 (14)	2 (18)	0.219	NS
CREAT>2	3 (14)	2 (18)	0.219	NS
Age				
Distribution				
AVERAGE	74	74.5		
MEDIAN	75	75.5		
MODE	77	81		
RANGE	62-87	58-83		

1 Patients with AVA decrease

2 Patients with either AVA increase or no change

§ Not applicable

TABLE 2

Mean AVA decrease in patients, according to presence or absence of risk factors

Risk factors	Present	Absent	t values	p values
HIST. OF HTN	0.41 +/- 0.14	0.23 +/- 0.18	0.102	NS
SMOKING	0.40 +/- 0.18	0.28 +/- 0.16	0.182	NS
CHOL>200	0.40 +/- 0.16	0.32 +/- 0.18	0.359	NS
HDL<29	0.28 +/- 0.18	0.36 +/- 0.17	0.53	NS
TRIG>16O	0.38 +/- 0.12	0.34 +/- 0.19	0.587	NS
NIDDM	0.45 +/- 0.07	0.34 +/- 0.18	0.654	NS
IDDM	0.15 *	0.36 +/- 0.17	§	§
BUN>40	0.33 +/- 0.21	0.35 +/- 0.17	0.861	NS
CREAT>2	0.33 +/- 0.21	0.35 =/- 0.17	0.861	NS

* Includes only one patient
§ Not applicable

TABLE 3

Two-tailed t values, p values and correlation coefficients in patients with AVA decrease, according to risk factors

Risk factors	t values	p values	Corr. Coeff.	# patients
HIST. of HTN	4.331 E-0.8	NS	0.51	14
SMOKING	0.0002	NS	0.26	9
CHOL>200	0.001	NS	0.21	7
HDL<29	0.272	NS	-0.17	2
TRIG>160	0.003	NS	0.13	6
NIDDM	0.07	NS	0.21	2
IDDM	*	*	-0.27	1
BUN>40	0.109	NS	-0.04	3
CREAT>2	0.109	NS	-0.04	3

* Includes only one patient

TABLE 4

Two-tailed t values, p values and correlation coefficients in patients with AVA decrease, according to the number of risk factors

# risk factors	t values	p values	Corr. Coeff.	# patients
5	0.374	NS	-0.1	2
4	0.07	NS	0.19	2
3	0.003	NS	0.07	5
2	0.0002	NS	0.5	6
1	0.118	NS	-0.28	3
0	0.05	NS	-0.53	3
				Total = 21

TABLE 5

Comparison between patients with increase in pk AV gd & those without, according to risk factors

	Subgroup C [1] (58 patients) # (%)	Subgroup D [2] (11 patients) # (%)	t values	p values
Risk factors				
HIST. OF HTN	41 (71)	8 (72)	0.634	NS
SMOKING	30 (52)	5 (45)	0.615	NS
CHOL>200	28 (48)	6 (55)	0.795	NS
HDL<29	4 (7)	0 (0)	§	§
TRIG>160	12 (21)	6 (55)	0.4	NS
NIDDM	6 (10)	1 (9)	§	§
IDDM	4 (7)	0 (0)	§	§
BUN>40	8 (14)	1 (9)	§	§
CREAT>2	8 (14)	3 (27)	0.28	NS
Age				
Distribution				
Average	72	74		
Median	72	74		
Mode	70	75		
Range	51-86	59-83		

1 Patients with pk AV gd increase

2 Patients with either pk Av gd decrease or no change

§ Not applicable

TABLE 6

Mean PK AV GD increase in patients, according to presence or absence of risk factors

Risk factors	Present	Absent	t values	p values
HIST. OF HTN	23 mmHg +/- 16	16 mmHg +/- 12	0.27	NS
SMOKING	24 mmHg +/- 17	25 mmHg +/- 26	0.409	Ns
CHOL>200	20 mmHg +/- 16	24 mmHg +/- 13	0.13	NS
HDL<29	22 mmHg +/- 19	22 mmHg +/- 14	1	NS
TRIG>160	22 mmHg +/- 14	22 mmHg +/- 15	1	NS
NIDDM	25 mmHg +/- 29	21 mmHG +/- 12	0.62	NS
IDDM	20 mmHg +/- 15	22 mmHg +/- 15	0.76	NS
BUN>40	20 mmHg +/- 13	22 mmHg +/- 15	0.76	NS
CREAT>2	20 mmHg +/- 14	22 mmHg +/- 15	0.65	NS

TABLE 7

Two-tailed t values, p values and correlation coefficients in patients with pk AV gd increase, according to risk factors

Risk factors	t values	p values	Corr. Coeff.	# patients
HIST. of HTN	1.341 E-11	NS	0.19	41
SMOKING	3.354 E-08	NS	0.13	30
CHOL>200	3.315 E-07	NS	-0.14	28
HDL<29	0.107	NS	0.001	4
TRIG>160	0.0003	NS	-0.001	12
NIDDM	0.094	NS	0.07	6
IDDM	0.081	NS	-0.04	4
BUN>40	0.004	NS	-0.04	8
CREAT>2	0.005	NS	-0.17	8

TABLE 8

Two-tailed t values, p values and correlation coefficients in patients with pk AV gd increase, according to the number of risk factors

# risk factors	t values	p values	Corr. Coeff.	# patients
6	*	*	0.12	1
5	0.162	NS	-0.09	4
4	0.002	NS	0.1	9
3	3.793 E-06	NS	-0.08	16
2	0.001	NS	0.12	11
1	0.0001	NS	-0.04	9
0	2.4 E-05	NS	-0.04	8
				Total = 58

* Includes only one patient

TABLE 9

Mean AVA decrease in patients, according to the number of risk factors present

# risk factors	Mean AVA decrease
5	0.3 +/- 0.28
4	0.45 +/- 0.07
3	0.37 +/- 0.13
2	0.48 +/- 0.12
1	0.23 +/- 0.15
0	0.13 +/- 0.06

TABLE 10

Mean PK AV GD increase in patients, according to the number of risk factors present

# risk factors	Mean pk AV gd increase
6	35 *
5	17 +/- 18
4	25 +/- 23
3	19 +/- 11
2	25 +/- 19
1	20 +/- 9
0	20 +/- 6

* Includes only one patient

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